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(54) Title: DRUGS FOR VASCULOPATIES

(57) Abstract: Use for the vasculopathy treatment of compounds or salts thereof, having the following general formula (I): wherein R is the radical of formula (AII), the radicals R_{AI}, R_1, and R_6 of formula (AII), and the bivalent linking groups B and C of the general (I) being as defined in the invention.

DRUGS FOR VASCULOPATHIES

* * * * *

The present invention relates to the use of drugs in the prevention and/or treatment of vasculopathies.

The most serious cardiovascular pathologies (among which restenosis, atherosclerosis, miocardium infarct, peripheral and central vascular diseases etc.) are characterized by a pathological activation of vascular cells (cells of the vasal smooth musculature cells, endothelial cells) and haematic cells (platelets, leucocytes, monocytes/macrophages, etc.).

Vasculopathies and diseases related thereto are pathological conditions associated to an altered haematochemical and clinical picture, which shows itself with hyperglycemia and/or hyperinsulinemia, hyperlipidemia and/or hydric-saline retention and/or hyperproliferation of vasal and/or tumoral cells, and/or prothrombotic and procoagulant activity, etc. Vasculopathies can facilitate the growth of other pathologies such obesity, diabetes and cardiovascular diseases such for example myocardial, cerebral and/or peripheral ischaemias, retinopathies, polyneuropathies, gastroenteropathies, nephropathies, etc., hypertension (general and local at pulmonary, coronary, portal, renal level, etc.) atherosclerosis, Alzheimer disease, cancer.

Also particular pathologies such as the X syndrome (or insulin resistance) and the vasculopathy from drugs are comprised in vasculopathies.

An unitary therapeutic approach able to prevent and/or reduce vasculopathies does not exist.

The ideal approach is to operate on the various cell processes, i.e. to prevent the pathological activation of the aforesaid cells, which causes the growth and the progress of the pathological process affecting the cardiovascular system.

At present the drugs used for vasculopathies and the used

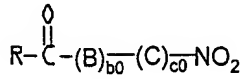
therapeutic approaches inhibit only one cell population, therefore they act only on one phase of the process, with only partially satisfactory results.

Statines, rapamycin and the radiotherapeutic treatment are active only on the smooth musculature but not on the other cell populations. The results obtained with said pharmacological treatments and with the radiotherapy are only partially satisfactory and therefore it is necessary to increase dosages with consequent even serious side effects.

The need was felt to have available drugs allowing to carry out an effective therapeutic treatment of vasculopathies, overcoming the drawbacks associated to the therapeutic and surgical treatments at present used, and being effective in inhibiting the pathological activation of various cell populations of the cardiovascular system and besides not resulting toxic, in particular at gastric level, and furthermore being usable for prolonged treatments without side effects.

This technical problem has been solved by the Applicant using a specific class of drugs. Surprisingly and unexpectedly the Applicant has found that specific nitrooxyderivatives of defined compounds, e.g. flurbiprofen, naproxen and diclofenac are active in the vasculopathy treatment, acting on the involved cell processes. Said result is surprising since other nitrooxyderivatives, such as for example the piroxicam and ketorolac derivatives, have not proved to be active at non toxic doses.

An object of the present invention is therefore the use in vasculopathies of drugs, or salts thereof, having the following general formula (I):



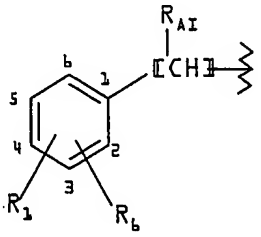
(I)

wherein:

c0 is an integer and is 0 or 1;

b0 is an integer and is 0 or 1, with the proviso that c0 and b0 cannot be contemporaneously equal to zero.

R is the radical of formula (AII)



(AII)

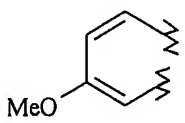
wherein:

R_{AI} is CH_3 or H;

R_1 is phenyl, or a 2,6-dichlorophenylamino- group;

R_6 is hydrogen or one halogen atom, preferably fluorine;

or R_1 and R_6 form together the radical of formula (AIa);



(AIa)

B = $-T_B-X_2-T_{BI}-$ wherein

T_B and T_{BI} are equal or different;

T_B = X, wherein X = O, S, NR_{1C}, R_{1C} is H or a linear or branched alkyl having from 1 to 5 carbon atoms ;

T_{BI} = $(CO)_{tx}$ or $(X)_{txx}$, wherein tx and txx have the value of 0 or 1; with the proviso that tx = 1 when txx = 0, tx = 0 when txx = 1; X is as above;

X_2, bivalent radical, is such that the corresponding precursor of B, $-T_B-X_2-T_{BI}-$ wherein the free valence of T_B is saturated with Z, and that of T_{BI} with OZ, Z

or with $-N(Z^I)(Z^{II})$, wherein Z = H, C_1-C_{10}, preferably C_1-C_5 alkyl linear or branched when possible, Z^I, Z^{II} equal or different have the values of Z as above, depending on that T_B and/or T_{BI} = CO or X, in function of the values of tx and txx;

the precursor compound of B being selected from the following:

- aminoacids, selected from the following: L-carnosine, anserine, selenocysteine, selenomethionine, penicillamine, N-acetylpenicillamine, cysteine, N-acetylcysteine, glutathione or its esters, preferably ethyl or isopropyl ester;
- hydroxyacids, selected from the following: gallic acid, ferulic acaid, gentisic acid, citric acid, caffeic, dihydrocaffeic acid, p-cumaric acid, vanillic acid;
- aromatic and hetrocyclic polyalcohols, selected from the following: nordihydroguaiaretic acid, quercetin, catechin, kaempferol, sulphurethyne, ascorbic acid, isoascorbic acid, hydroquinone, gossypol, reductic acid, methoxyhydroquinone, hydroxyhydroquinone, propyl gallate, saccharose, 3,5-di-tertbutyl-4-hydroxybenzyl-thio glycolate, p-cumaric alcohol, 4-hydroxyphenylethylalcohol, coniferyl alcohol, allopurinol;
- compounds containing at least one free acid function, selected from the following: 3,3'-thiodipropionic acid, fumaric acid, dihydroxymaleic acid, edetic acid;

C is the bivalent radical $-T_c-Y-$ wherein

when b0 = c0 = 1: T_c = (CO) when tx = 0, T_c = X when txx = 0, X being as above defined,

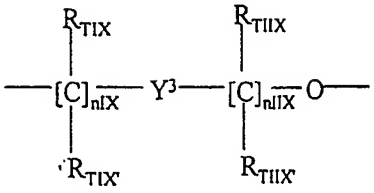
when b0 = 0 : T_c = X, X being as above defi-

ned,

when c0 = 0 : tx = 0, T_{BI} = X = –O–;

Y is:

Y_p :



(III)

wherein:

nIX is an integer comprised between 0 and 3, preferably 1;

nIIX is an integer comprised between 1 and 3, preferably 1;

R_{TIX}, $R_{TIX'}$, R_{TIIX}, $R_{TIIX'}$, equal to or different from each other are H or linear or branched C_1-C_4 alkyl; preferably R_{TIX}, $R_{TIX'}$, R_{TIIX}, $R_{TIIX'}$ are H.

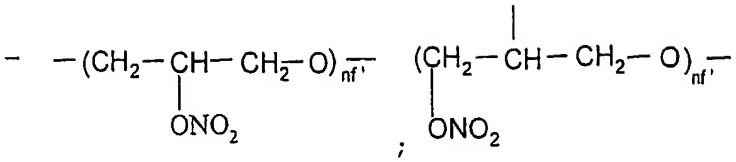
Y^3 is a saturated, unsaturated or aromatic heterocyclic ring containing one or two nitrogen atoms, having 5 or 6 atoms,

or Y can be:

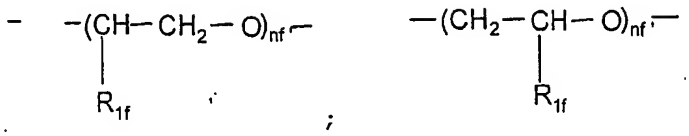
Y_0, selected from the following:

- an alkylenoxy group R'O wherein R' is a linear or branched when possible C_1-C_{20}, preferably having from 2 to 6 carbon atoms, or a cycloalkylene having from 5 to 7 carbon atoms, in the cycloalkylene ring one or more carbon atoms can be substituted by heteroatoms, the ring can have side chains of R' type, R' being as above;

or one of the following groups:

- 
;

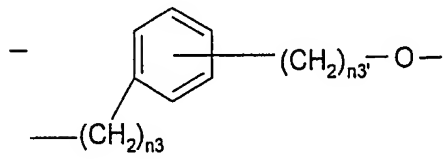
wherein nf' is an integer from 1 to 6 preferably from 1 to 4;

- 
;

wherein R_{1f} = H, CH_3 and nf' is an integer from 1 to 6; preferably from 1 to 4;

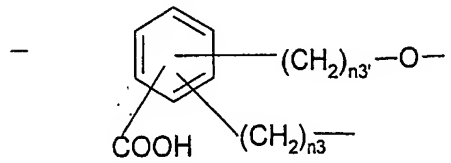
or Y is Y_{AR} and is selected from the following:

Y_{AR1} :



wherein n3 is an integer from 0 to 3 and n3' is an integer from 1 to 3;

Y_{AR2} :



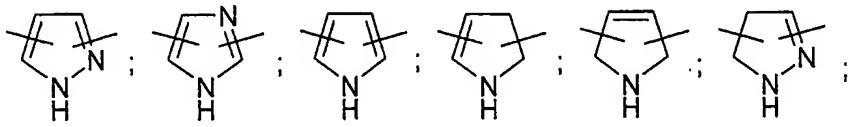
wherein n3 and n3' have the above meaning.

When in formula (AII) R_{AI} is CH_3, R_1 is the phenyl group in position 4 of the ring, R_6 = F in position 3, the so defined radical is that of the precursor drug Flurbiprofen;

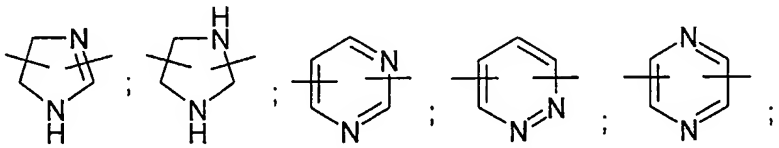
when in formula (AII) R_{AI} is CH_3, R_1 and R_6 are in position 4 and 5 of the ring and form together the radical of formula (AIa), the so defined radical is that of the precursor drug Naproxen;

when in formula (AII) R_{AI} is H, R_1 is the 2,6-dichlorophenylamino group and is in position 2 of the ring, R_6 = H, the so defined radical is that of the precursor drug Diclofenac.

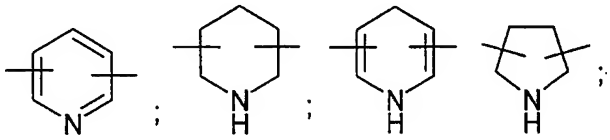
Preferably Y^3 is selected from the following:



(Y1) (Y2) (Y3) (Y4) (Y5) (Y6)



(Y7) (Y8) (Y9) (Y10) (Y11)



(Y12) (Y13) (Y14) (Y15)

Preferably Y^3 is an aromatic ring having 6 atoms, containing one nitrogen atom, said aromatic ring having the two free valences in position 2 and 6.

The preferred of Y^3 is Y12 (pyridyl) substituted in position 2 and 6. The bonds can also be in an asymmetric position, for example Y12 (pyridyl) can be substituted also in position 2 and 3; Y1 (pyrazol) can be 3,5-disubstituted.

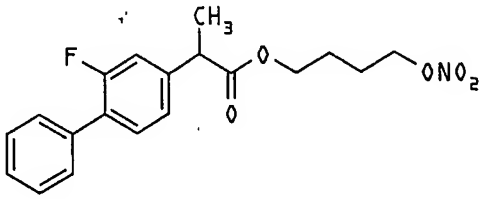
The precursors of Y_p, wherein the oxygen free valence is saturated with H and the free valence of the end carbon is saturated either with a carboxylic or an hydroxyl group, are compounds available on the market or can be obtained by methods known in the prior art.

The functional linking groups between, respectively, R and X_2, between X_2 and Y, or between R and Y, can be ester, amideor thioester.

The precursor compounds of B of the above groups are prepard according to the methods known in the prior art and described for example in "The Merck Index", 12th Ed. (1996), herein incorporated by reference.

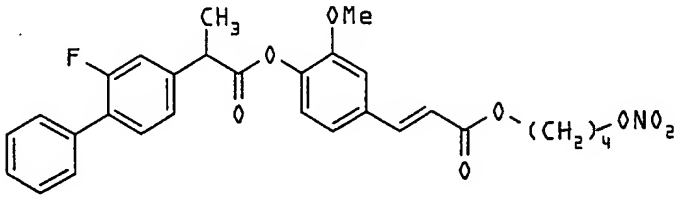
The preferred compounds of formula (I) are the following:

2-Fluoro-α-methyl[1,1'-biphenyl]-4-acetic acid 4-(nitrooxy) butyl ester (V)



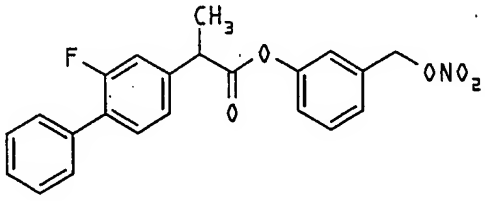
(V)

Trans-3-[4-[2-fluoro-alpha-methyl(1,1'-biphenyl)-4-acetyl oxy]-3-methoxyphenyl]-2-propenoic acid 4-(nitrooxy)butyl ester (VI)



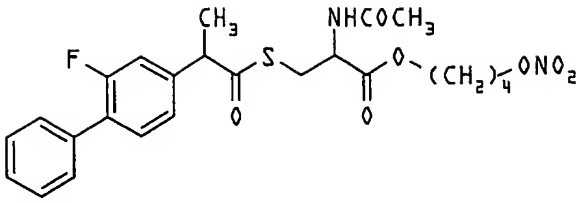
(VI)

2-fluoro-alpha-methyl[1,1'-biphenyl]-4-acetic acid 3-(nitrooxy methyl)phenyl ester (VII)



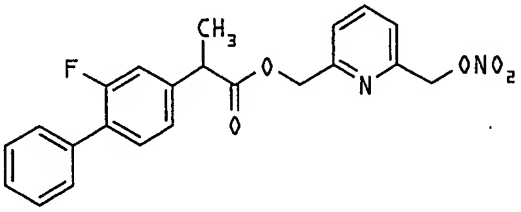
(VII)

(S)-N-acetyl-S-[2-fluoro-alpha-methyl(1,1'-biphenyl)-4-acetyl]cysteine 4-(nitrooxy)butyl ester (VIII)



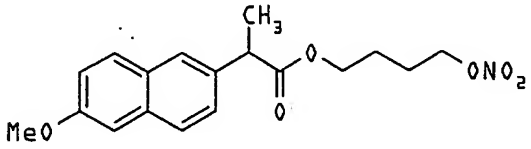
(VIII)

2-fluoro-alpha-methyl[1,1'-biphenyl]-4-acetic acid 6-(nitrooxy methyl)-2-methylpyridinyl ester (IX)



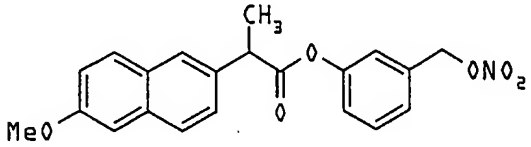
(IX)

(S)-6-methoxy-alpha-methyl-2-naphthalenacetic acid 4-(nitrooxy)butyl ester (X)



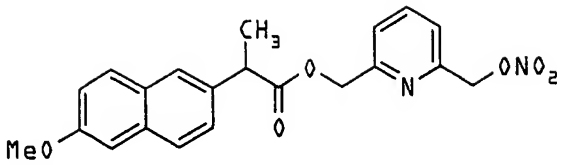
(X)

(S)-6-methoxy-alpha-methyl-2-naphthalenacetic acid 3-(nitrooxy methyl)phenyl ester (XI)



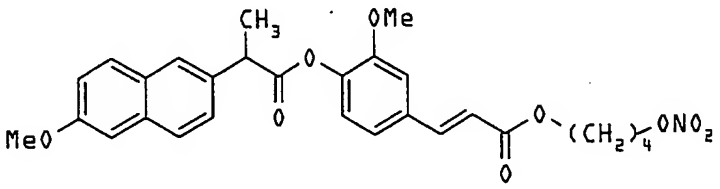
(XI)

(S)-6-methoxy-alpha-methyl-2-naphthalenacetic acid 6-(nitrooxymethyl)-2-methylpyridinyl ester (XII)



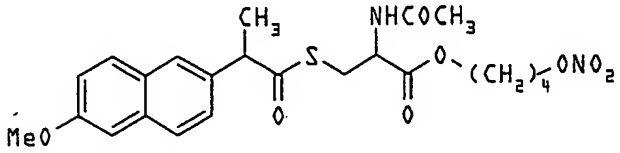
(XII)

Trans-3-[4-[6-methoxy-alpha-methyl-2-naphthalenacetyl oxy]-3-methoxyphenyl]-2-propenoic acid 4-(nitrooxy)butyl ester (XIII)



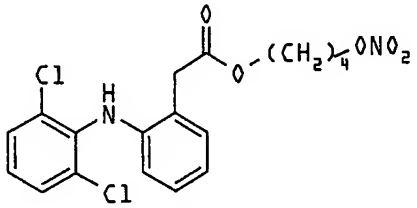
(XIII)

(S,S)-N-acetyl-S-(6-methoxy-alpha-methyl-2-naphthalena-cetyl) cysteine 4-(nitrooxy)butyl ester (XIV)



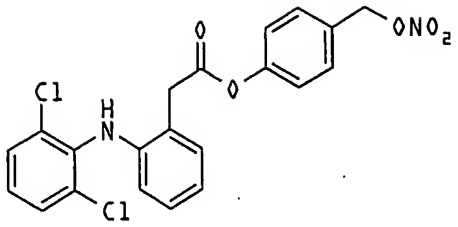
(XIV)

2-[(2,6-dichlorophenyl)amino]benzenacetic acid 4-(nitrooxy) butyl ester (XV)



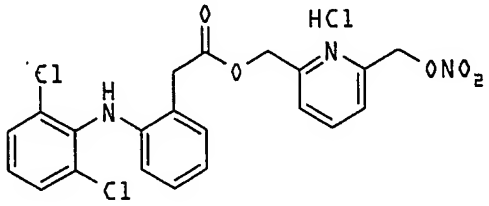
(XV)

2-[(2,6-dichlorophenyl)amino]benzenacetic acid 4-(nitro oxymethyl)phenyl ester (XVI)



(XVI)

2-[(2,6-dichlorophenyl)amino]benzenacetic acid 6-(nitro oxymethyl)-2-methylpyridinyl hydrochloride ester (XVII)



(XVII)

The compounds of formula (I) are generally obtained by methods known in the prior art, see for example patent applications WO 00/61537, WO 00/51988, WO 95/30641, in the name of the Applicant.

When the compounds of formula (I) usable in the present invention have one or more chiral centres, they can be in a racemic form or as mixtures of diastereoisomers, as single enantiomers or single diastereoisomers; when they show a geometric asymmetry, the compounds in the cis or trans form can be used.

When in the molecule of the compounds of formula (I) a salifiable functional group is present, for example an aminic or heterocyclic nitrogen, it is possible to use the corresponding salts of the above compounds, obtainable by reaction in organic solvent such as for example acetonitrile, tetrahydrofuran, with an equimolar amount of the corresponding organic or inorganic acid.

Examples of usable organic acids are the following: oxalic, tartaric, maleic, succinic, citric acids.

Examples of usable inorganic acids are the following: nitric, hydrochloric, sulphuric, phosphoric acids. Nitric and hydrochloric acids are preferred.

By using the products of the invention the vasculopathy is significantly reduced and in particular the restenosis process which can grow in people subjected to angioplasty and in particular in those more at risk such as old people, diabetic, hyperlipidemic people.

The therapeutic use of the products described in the present invention results advantageous, as said, since these compounds are able to act both on the duct (endothelial and vasal smooth musculature cells) and on haematic cells (platelets, leucocytes) and haematic factors.

The compounds of formula (I) or the corresponding salts are formulated in the corresponding pharmaceutical compositions for parenteral, oral use according to the techniques well known in the prior art, together with the usual excipients; see for example the volume "Remington's Pharmaceutical Sciences 15th Ed.".

The amount on a molar basis of the active principle in said formulations is equal to or lower than the maximum posology indicated for the precursor drugs. Also higher doses can be used considering their very good tolerability. The daily doses of the precursor drugs can be found in the publications of the prior art, such as for example in "Physician's Desk reference".

The following Examples illustrate the invention but are not limitative of the scope of the same.

EXAMPLE F1

Efficacy of Flurbiprofen and of 2-fluoro-alpha-methyl-4-diphenylacetic acid (4-nitrooxy) butyl ester in an experimental model of restenosis induced in rats

2-fluoro-alpha-methyl-4-diphenylacetic acid (4-nitrooxy)butyl ester (NO-Flurbiprofen) was synthesized as described in Example 1 of patent application WO 95/30641.

Wistar male rats of 300-350 g weight were anaesthetized by intraperitoneal injection of ketamine (100 mg/kg) and xylazine (5 mg/kg) and subjected to angioplasty according to the procedure described by Indolfi et Al., Circulation 1995 92 1230-1235, by using a little balloon catheter. The balloon was first introduced in the aortic arch through the right carotid, then swollen and passed three times forth and back in the duct lumen.

After the vascular damage the animals were divided in the two groups indicated below and subjected for 14 days to the pharmacological treatment as described hereunder: one group was treated by os by means of a gastric cannula with NO-Flurbiprofen at the dose of 10 mg/kg dissolved in polyethylene glycol (PEG 400), and the other group (control) received only the carrier (PEG 400, 0.2 ml/rat).

The animals were sacrificed and the carotids removed. For each artery no. 6 sections having a thickness of 6 μm were obtained. Stomachs were also removed and inspected to evaluate damages to the gastric mucosa. Areas of both bleeding lesions and non bleeding lesions were determined.

3 out of the 6 sections of each artery were stained with hematoxylin and eosin to evidence the different types of cells, the remaining 3 sections were stained first with aldehyde fuchsin and then with the Gieson solution to evidence the internal elastic lamina. The sections were photographed

and the imagines were analyzed by an image analysis system (Qwin Lite, Leica, Milan).

The thicknesses, respectively, of the middle and neointima tunica, and of the duct wall were measured. The results reported in Table 1 are expressed as percentage of restenosis and have been calculated as a ratio between the thickness of the neointima tunica to that of the middle tunica (M/N) measured in the sections of the various groups, assuming equal to 100 the N/M ratio of the control group.

The results are reported in Table 1.

EXAMPLE F2

Example F1 is repeated but using NO-Flurbiprofen at the dose of 30 mg/Kg. The results are reported in Table 1.

EXAMPLE F3 Comparative

Example F1 is repeated but using Flurbiprofen at the dose of 7 mg/Kg. The results are reported in Table 1.

EXAMPLE F4 Comparative

Example F1 is repeated but using Flurbiprofen at the dose of 21 mg/Kg. The results are reported in Table 1.

EXAMPLE F5 Comparative

In this Example the 5-benzoyl-2,3-dihydro-1H-pyrrolidin-1-carboxylic acid (4-nitrooxy)butyl ester (NO-ketorolac) is used, sinthesized as described in Example 1F of patent application WO 95/30641.

Example F1 is repeated but using NO-Ketorolac at the dose of 10 mg/Kg.

Comments on Table 1

The results reported in Table 1 show that the restenosis induced by the lesion with the little balloon catheter is significantly reduced by administering low doses of NO-Flurbiprofen. Flurbiprofen is not very effective in reducing restenosis even at the dose of 20 mg/Kg. The number of gastric lesions following administration of Flurbiprofen is very

high in the confront of NO-Flurbiprofen.

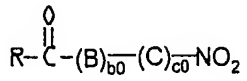
NO-Ketorolac appears not very effective with respect to NO-Flurbiprofen and at effective doses it produces gastric lesions.

Table 1

Activity of the compounds of Example F1 on the restenosis experimentally caused by balloon angioplasty and evaluation of the damages to the gastric mucosa caused by administering the tested compounds (* = p<0.05 vs controls)				
Compounds	Dose (mg/Kg)	Restenosis %	Dose (mg/Kg)	Gastric damage Score
Control	--	100	--	2
NO-Flurbiprofen (Ex. F1)	10	63*	10	1
NO Flurbi-profen (Ex. F2)	30	54*	30	5
Flurbiprofen (Ex. F3 comp)	10	98	10	23*
Flurbiprofen (Ex. F4 comp)	20	87	20	38
NO Ketorolac (Ex. F5 comp)	10	90	10	20

CLAIMS

1. Use for the preparation of drugs for the vasculopathy treatment, of compounds, or salts thereof, having the following general formula (I):



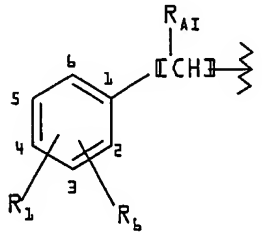
(I)

wherein:

c0 is an integer and is 0 or 1;

b0 is an integer and is 0 or 1, with the proviso that c0 and b0 cannot be contemporaneously equal to zero.

R is the radical of formula (AII)



(AII)

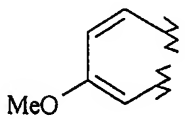
wherein:

R_{AI} is CH_3 or H;

R_1 is phenyl, or a 2,6-dichlorophenylamino- group;

R_6 is hydrogen or one halogen atom, preferably fluorine;

or R_1 and R_6 form together the radical of formula (AIa);



(AIa)

B = $-T_B-X_2-T_{BI}-$ wherein

T_B and T_{BI} are equal or different;
T_B = X, wherein X = O, S, NR_{1C}, R_{1C} is H or a linear or banched alkyl having from 1 to 5 carbon atoms;
T_{BI} = $(CO)_{tx}$ or $(X)_{txx}$, wherein tx and txx have the value of 0 or 1; with the proviso that tx = 1 when txx = 0, tx = 0 when txx = 1; X is as above;
X_2, bivalent radical, is such that the corresponding precursor of B, $-T_B-X_2-T_{BI}-$ wherein the free valence of T_B is saturated with Z, and that of T_{BI} with OZ, Z or with $-N(Z^I)(Z^{II})$, wherein Z = H, C_1-C_{10}, preferably C_1-C_5 alkyl linear or branched when possible, Z^I, Z^{II} equal or different have the values of Z as above, depending on that T_B and/or T_{BI} = CO or X, in function of the values of tx and txx;
the precursor compound of B being selected from the following:

- aminoacids, selected from the following: L-carnosine, anserine, selenocysteine, selenomethionine, penicillamine, N-acetylpenicillamine, cysteine, N-acetilcysteine, glutathione or its esters, preferably ethyl or isopropyl ester;
- hydroxyacids, selected from the following: gallic acid, ferulic acid, gentisic acid, citric acid, caffeic, dihydrocaffeic acid, p-cumaric acid, vanillic acid;
- aromatic and heterocyclic polyalcohols, selected from the following: nordihydroguaiaretic acid, quercetin, catechin, kaempferol, sulphurethyne, ascorbic acid, isoascorbic acid, hydroquinone, gossypol, reductic acid, methoxyhydroquinone, hydroxyhydroquinone, propyl gallate, saccharose, 3,5-di-tertbutyl-4-hydroxybenzyl-thio glycolate, p-cumaric alcohol, 4-hydroxy-phenylethylalcohol, coniferyl

alcohol, allopurinol;

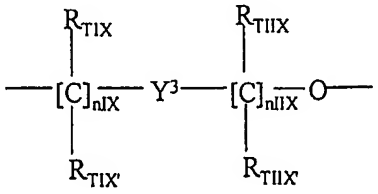
- compounds containing at least one free acid function, selected from the following: 3,3'-thiodipropionic acid, fumaric acid, dihydroxy-maleic acid, edetic acid;

C being the bivalent radical $-T_c-Y-$ wherein

T_c = (CO) when tx = 0, T_c = X when txx = 0, X being as above defined;

Y is:

Y_p :



(III).

wherein:

nIX is an integer comprised between 0 and 3, preferably 1;

nIIX is an integer comprised between 1 and 3, preferably 1;

R_{TIX}, $R_{TIX'}$, R_{TIIX}, $R_{TIIX'}$, equal to or different from each other are H or linear or branched C_1-C_4 alkyl; preferably R_{TIX}, $R_{TIX'}$, R_{TIIX}, $R_{TIIX'}$ are H.

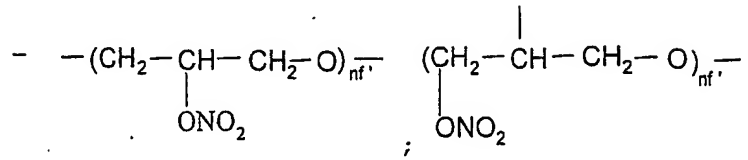
Y^3 is a saturated, unsaturated or aromatic heterocyclic ring containing one or two nitrogen atoms, having 5 or 6 atoms,

or Y can be:

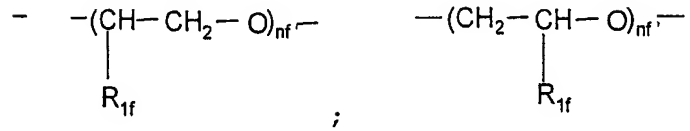
Y_0, selected from the following:

- an alkylenoxy group R'O wherein R' is a linear or branched when possible C_1-C_{20}, preferably having from 2 to 6 carbon atoms, or a cycloalkylene having from 5 to 7 carbon atoms, in the cycloalkylene ring one or more carbon atoms can be substituted by het-

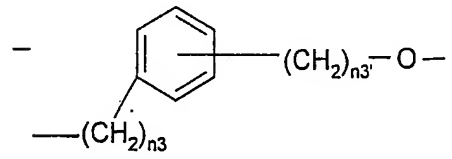
eroatoms, the ring can have side chains of R' type, R' being as above;
or one of the following groups:



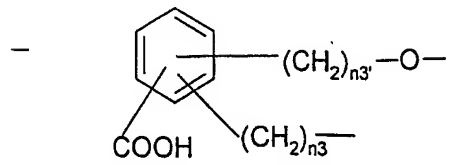
wherein nf' is an integer from 1 to 6 preferably from 1 to 4;



wherein R_{1f} = H, CH_3 and nf' is an integer from 1 to 6; preferably from 1 to 4;
or Y is Y_{AR} and is selected from the following:
Y_{AR1} :



wherein n3 is an integer from 0 to 3 and n3' is an integer from 1 to 3;
Y_{AR2} :



wherein n3 and n3' have the above meaning.

2. Use according to claim 1, wherein:

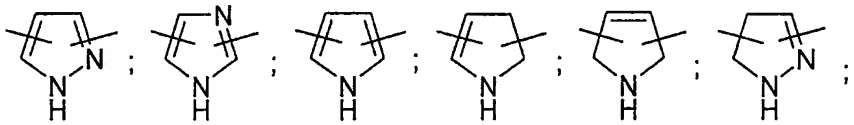
when in formula (AII) R_{AI} is CH_3, R_1 is the phenyl group in position 4 of the ring, R_6 = F in position 3, the so defined radical is that of the precursor drug

Flurbiprofen;

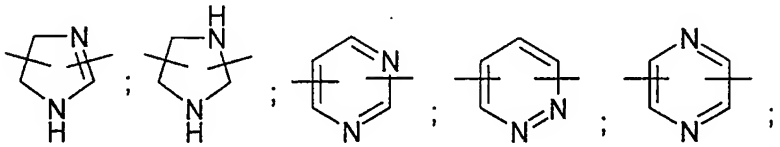
when in formula (AII) R_{AI} is CH_3, R_1 and R_6 are in position 4 and 5 of the ring and form together the radical of formula (AIa), the so defined radical is that of the precursor drug Naproxen;

when in formula (AII) R_{AI} is H, R_1 is the 2,6-dichlorophenylamino- group and is in position 2 of the ring, R_6 = H, the so defined radical is that of the precursor drug Diclofenac.

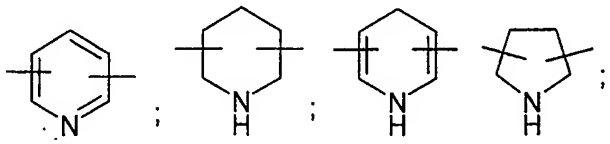
3. Use according to claims 1-2, wherein Y^3 is selected from the following:



(Y1) (Y2) (Y3) (Y4) (Y5) (Y6)



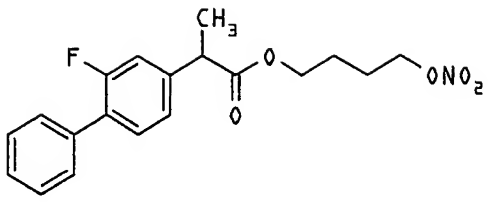
(Y7) (Y8) (Y9) (Y10) (Y11)



(Y12) (Y13) (Y14) (Y15)

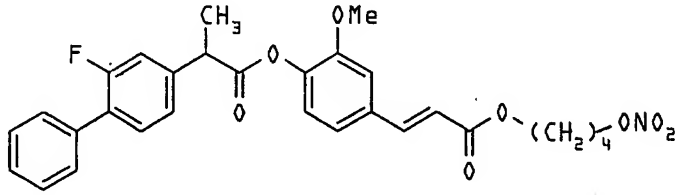
4. Use according to claim 3, wherein Y^3 is an aromatic ring having 6 atoms, containing one nitrogen atom, having the two free valences in position 2 and 6.
5. Use according to claims 3-4, wherein Y^3 is Y12 (pyridyl).
6. Use according to claims 1-5, wherein the preferred compounds of formula (I) are the following:

2-Fluoro-α-methyl[1,1'-biphenyl]-4-acetic acid 4-(nitrooxy) butyl ester (V)



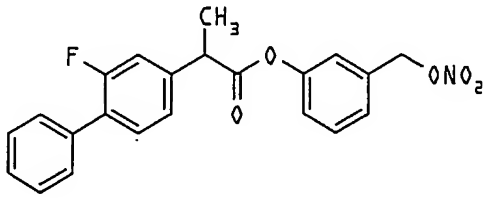
(V)

Trans-3-[4-[2-fluoro-alpha-methyl(1,1'-biphenyl)-4-acetyloxy]-3-methoxyphenyl]-2-propenoic acid 4-(nitrooxy) butyl ester (VI)



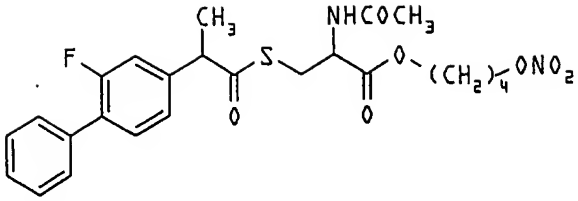
(VI)

2-Fluoro-alpha-methyl[1,1'-biphenyl]-4-acetic acid 3-(nitrooxy methyl)phenyl ester (VII)



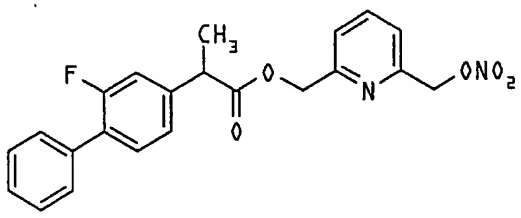
(VII)

(S)-N-acetyl-S-[2-fluoro-alpha-methyl(1,1'-biphenyl)-4-acetyl]cysteine 4-(nitrooxy)butyl ester (VIII)



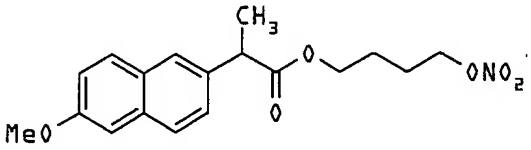
(VIII)

2-Fluoro-alpha-methyl[1,1'-biphenyl]-4-acetic acid 6-(nitrooxy methyl)-2-methylpyridinyl ester (IX)



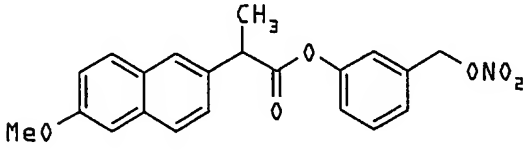
(IX)

(S)-6-methoxy-alpha-methyl-2-naphthalenacetic acid 4-(nitrooxy)butyl ester (X)



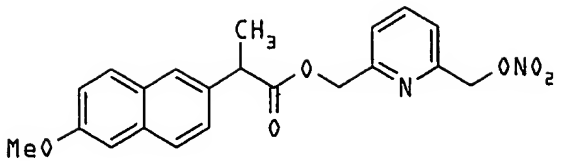
(X)

(S)-6-methoxy-alpha-methyl-2-naphthalenacetic acid 3-(nitrooxy methyl)phenyl ester (XI)



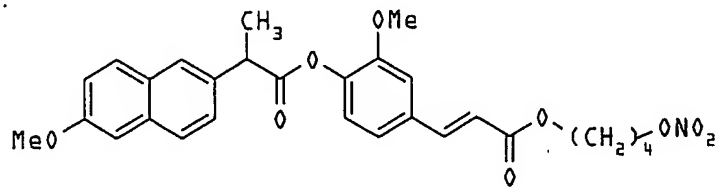
(XI)

(S)-6-methoxy-alpha-methyl-2-naphthalenacetic acid 6-(nitrooxymethyl)-2-methylpyridinyl ester (XII)



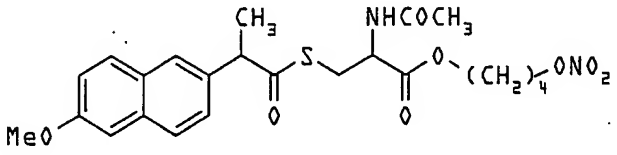
(XII)

Trans-3-[4-[6-methoxy-alpha-methyl-2-naphthalen acetyloxy]-3-methoxyphenyl]-2-propenoic acid 4-(nitrooxy) butyl ester (XIII)



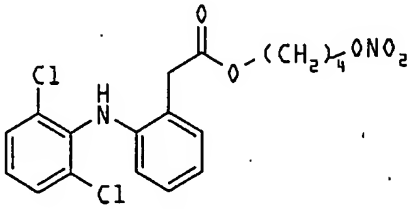
(XIII)

(S,S)-N-acetyl-S-(6-methoxy-alpha-methyl-2-naphthalene acetyl) cysteine 4-(nitrooxy)butyl ester (XIV)



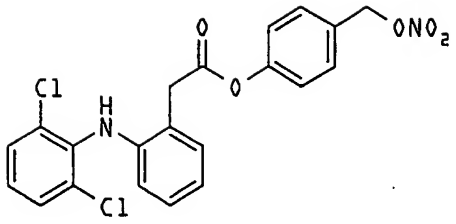
(XIV)

2-[(2,6-dichlorophenyl)amino]benzenacetic acid 4-(nitrooxy)butyl ester (XV)



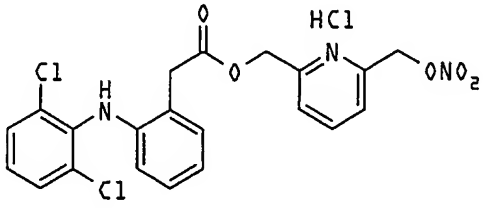
(XV)

2-[(2,6-dichlorophenyl)amino]benzenacetic acid 4-(nitrooxymethyl)phenyl ester (XVI)



(XVI)

2-[(2,6-dichlorophenyl)amino]benzenacetic acid 6-(nitrooxymethyl)-2-methylpyridinyl hydrochloride ester (XVII)



(XVII)

7. Use according to claims 1-6, wherein the compounds of formula (I) or the corresponding salts are formulated in the corresponding pharmaceutical compositions for parenteral, oral use.